



Year: 2019

Blood Purification and Mortality in Sepsis and Septic Shock: A Systematic Review and Meta-analysis of Randomized Trials

Putzu, Alessandro ; Schorer, Raoul ; Lopez-Delgado, Juan Carlos ; Cassina, Tiziano ; Landoni, Giovanni

Abstract: BACKGROUND Sepsis and septic shock are severe inflammatory conditions related to high morbidity and mortality. We performed a systematic review with meta-analysis of randomized trials to assess whether extracorporeal blood purification reduces mortality in this setting. METHODS Electronic databases were searched for pertinent studies up to January 2019. We included randomized controlled trials on the use of hemoperfusion, hemofiltration without a renal replacement purpose, and plasmapheresis as a blood purification technique in comparison to conventional therapy in adult patients with sepsis and septic shock. The primary outcome was mortality at the longest follow-up available. We calculated relative risks and 95% CIs. The grading of recommendations assessment, development and evaluation methodology for the certainty of evidence was used. RESULTS Thirty-seven trials with 2,499 patients were included in the meta-analysis. Hemoperfusion was associated with lower mortality compared to conventional therapy (relative risk = 0.88 [95% CI, 0.78 to 0.98], $P = 0.02$, very low certainty evidence). Low risk of bias trials on polymyxin B immobilized filter hemoperfusion showed no mortality difference versus control (relative risk = 1.14 [95% CI, 0.96 to 1.36], $P = 0.12$, moderate certainty evidence), while recent trials found an increased mortality (relative risk = 1.22 [95% CI, 1.03 to 1.45], $P = 0.02$, low certainty evidence); trials performed in the United States and Europe had no significant difference in mortality (relative risk = 1.13 [95% CI, 0.96 to 1.34], $P = 0.15$), while trials performed in Asia had a positive treatment effect (relative risk = 0.57 [95% CI, 0.47 to 0.69], $P < 0.001$). Hemofiltration (relative risk = 0.79 [95% CI, 0.63 to 1.00], $P = 0.05$, very low certainty evidence) and plasmapheresis (relative risk = 0.63 [95% CI, 0.42 to 0.96], $P = 0.03$, very low certainty evidence) were associated with a lower mortality. CONCLUSIONS Very low-quality randomized evidence demonstrates that the use of hemoperfusion, hemofiltration, or plasmapheresis may reduce mortality in sepsis or septic shock. Existing evidence of moderate quality and certainty does not provide any support for a difference in mortality using polymyxin B hemoperfusion. Further high-quality randomized trials are needed before systematic implementation of these therapies in clinical practice.

DOI: <https://doi.org/10.1097/ALN.0000000000002820>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-180579>

Journal Article

Published Version

Originally published at:

Putzu, Alessandro; Schorer, Raoul; Lopez-Delgado, Juan Carlos; Cassina, Tiziano; Landoni, Giovanni (2019). Blood Purification and Mortality in Sepsis and Septic Shock: A Systematic Review and Meta-analysis of Randomized Trials. *Anesthesiology*, 131(3):580-593.

DOI: <https://doi.org/10.1097/ALN.0000000000002820>

ANESTHESIOLOGY

Blood Purification and Mortality in Sepsis and Septic Shock

A Systematic Review and Meta-analysis of Randomized Trials

Alessandro Putzu, M.D., Raoul Schorer, M.D.,
Juan Carlos Lopez-Delgado, M.D., Ph.D.,
Tiziano Cassina, M.D., Giovanni Landoni, M.D.

ANESTHESIOLOGY 2019; 131:580–93

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Among patients with sepsis or septic shock, a variety of extracorporeal blood purification techniques are available
- Individual existing trials evaluating these options are underpowered to provide clear evidence

What This Article Tells Us That Is New

- Meta-analysis of very low-quality randomized controlled trial evidence demonstrates a potential benefit of hemoperfusion, hemofiltration, or plasmapheresis
- Additional high-quality trials demonstrating benefit in modern clinical practice are needed before recommending these therapies

Today, sepsis remains one of the main causes of morbidity and mortality in the intensive care unit. Despite recent advancement in intensive care unit and sepsis management, mortality still remains high.^{1–4}

The pathogenesis of sepsis involves many complex cellular and biochemical interactions between leukocytes, platelets, endothelial cells, and the complement system that trigger an inflammatory response.⁵ Inflammation is caused by the production of pro- and antiinflammatory mediators, such as cytokines, in the presence of infection and/or bacterial toxins, and the imbalance between these mediators or

ABSTRACT

Background: Sepsis and septic shock are severe inflammatory conditions related to high morbidity and mortality. We performed a systematic review with meta-analysis of randomized trials to assess whether extracorporeal blood purification reduces mortality in this setting.

Methods: Electronic databases were searched for pertinent studies up to January 2019. We included randomized controlled trials on the use of hemoperfusion, hemofiltration without a renal replacement purpose, and plasmapheresis as a blood purification technique in comparison to conventional therapy in adult patients with sepsis and septic shock. The primary outcome was mortality at the longest follow-up available. We calculated relative risks and 95% CIs. The grading of recommendations assessment, development and evaluation methodology for the certainty of evidence was used.

Results: Thirty-seven trials with 2,499 patients were included in the meta-analysis. Hemoperfusion was associated with lower mortality compared to conventional therapy (relative risk = 0.88 [95% CI, 0.78 to 0.98], $P = 0.02$, very low certainty evidence). Low risk of bias trials on polymyxin B immobilized filter hemoperfusion showed no mortality difference versus control (relative risk = 1.14 [95% CI, 0.96 to 1.36], $P = 0.12$, moderate certainty evidence), while recent trials found an increased mortality (relative risk = 1.22 [95% CI, 1.03 to 1.45], $P = 0.02$, low certainty evidence); trials performed in the United States and Europe had no significant difference in mortality (relative risk = 1.13 [95% CI, 0.96 to 1.34], $P = 0.15$), while trials performed in Asia had a positive treatment effect (relative risk = 0.57 [95% CI, 0.47 to 0.69], $P < 0.001$). Hemofiltration (relative risk = 0.79 [95% CI, 0.63 to 1.00], $P = 0.05$, very low certainty evidence) and plasmapheresis (relative risk = 0.63 [95% CI, 0.42 to 0.96], $P = 0.03$, very low certainty evidence) were associated with a lower mortality.

Conclusions: Very low-quality randomized evidence demonstrates that the use of hemoperfusion, hemofiltration, or plasmapheresis may reduce mortality in sepsis or septic shock. Existing evidence of moderate quality and certainty does not provide any support for a difference in mortality using polymyxin B hemoperfusion. Further high-quality randomized trials are needed before systematic implementation of these therapies in clinical practice.

(*ANESTHESIOLOGY* 2019; 131:580–93)

their excessive production may lead to multiorgan failure due to a prolonged or inadequate systemic inflammatory response syndrome.^{5,6}

Extracorporeal blood purification techniques have been proposed as adjunctive therapy in sepsis. These techniques are based on the principle that removal and modulation of blood pro- and antiinflammatory mediators or bacterial toxins (or both) could attenuate the sepsis-related massive

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). For a downloadable PPT slide containing this article's citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx.

Submitted for publication September 26, 2018. Accepted for publication April 23, 2019. From the Division of Anesthesiology, Department of Anesthesiology, Pharmacology, Intensive Care, and Emergency Medicine, Geneva University Hospitals, Geneva, Switzerland (A.P., R.S.); the Hospital Universitari de Bellvitge, Intensive Care Department, and the Biomedical Investigation Institute of Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain (J.C.L.-D.); the Department of Cardiovascular Anesthesia and Intensive Care, Cardiocentro Ticino, Lugano, Switzerland (T.C.); the Department of Anaesthesia and Intensive Care, San Raffaele Scientific Institute, Milan, Italy (G.L.); and Vita-Salute San Raffaele University, Milan, Italy (G.L.).

Copyright © 2019, the American Society of Anesthesiologists, Inc. All Rights Reserved. *Anesthesiology* 2019; 131:580–93. DOI: 10.1097/ALN.0000000000002820

systemic inflammatory response, reducing morbidity and mortality.^{7,8} Several different extracorporeal techniques have been studied for this purpose.

Hemoperfusion involves the placement of a sorbent cartridge in direct contact with blood *via* an extracorporeal circuit. The removal characteristics of hemoperfusion are dependent on the different types of sorbent used and could also target high-molecular-weight molecules, usually not captured by conventional hemofilters. The most studied therapy is polymyxin B immobilized fiber column hemoperfusion with Toraymyxin (Toray Industries Ltd., Japan), that could capture circulating bacterial endotoxin⁹ and modulate the inflammatory response.¹⁰ Another device is the CytoSorb (CytoSorbents Corporation, USA), a novel filter potentially able to remove both pro-inflammatory and antiinflammatory cytokines.¹¹

Renal replacement devices such as hemofiltration or hemodiafiltration could be used to remove part of the inflammatory mediators and toxins in septic patients without renal indication for kidney replacement therapy, by employing standard or special filters with adsorptive properties.¹² Limited data are available on plasmapheresis, a technique based on plasma replacement with fresh frozen plasma or albumin,¹² that has the potential to remove inflammatory cytokines and restore deficient plasma proteins.

Despite the large number of available techniques, actual evidence is scarce, and these therapies have not entered into daily clinical practice around the world yet. Several small trials were published on various devices, and the most comprehensive meta-analysis summarizing the evidence on blood purification is outdated.¹³ Some more recent meta-analyses focusing on polymyxin B immobilized fiber column hemoperfusion^{14,15} or hemofiltration¹⁶ did not include some relevant trials nor the final results of the largest randomized study performed on the topic so far.¹⁷ Therefore, we performed a meta-analysis of randomized control trials in order to determine whether extracorporeal blood purification decreased mortality in patients with sepsis and septic shock.

Materials and Methods

The current systematic review was conducted in compliance with the PRISMA (Preferred Reporting Items Systematic Reviews and Meta-Analysis) guidelines¹⁸ (Supplemental Digital Content, table S1, <http://links.lww.com/ALN/B977>) and Cochrane methodology¹⁹ and according to a prepublished protocol (PROSPERO database, CRD42018104643).

Search Strategy

Two investigators (A.P. and R.S.) independently searched PubMed, the Cochrane Central Register of clinical trials, and Embase up to January 1, 2019, for relevant articles (Supplemental Digital Content, table S2, <http://links.lww.com/ALN/B977>).

The search strategy aimed to include any randomized study performed with any type of extracorporeal blood purification technique compared to conventional therapy in adult critically ill patients with sepsis and septic shock. Abstracts from recent international conferences were searched for additional studies. In addition, we hand-scanned references of retrieved articles and pertinent reviews to identify other eligible trials (backward snowballing).

Study Selection

References obtained from searches were first independently examined at the abstract level by two authors (A.P. and R.S.) and then collected as full-text articles if potentially relevant. Eligible studies met the following PICOS criteria: (1) Population: adult critically ill patients with sepsis with or without septic shock; (2) Intervention: any extracorporeal blood purification technique (hemoperfusion, renal replacement therapy techniques, plasmapheresis); (3) Comparison intervention: conventional therapy; (4) Outcome: mortality at longest follow-up available; and (5) Study design: randomized controlled trial. The exclusion criteria were blood purification for renal failure indication at randomization, trials with overlapping populations with a previously included article (*e.g.*, manuscripts with different follow-up or subanalyses of a previously published trial), and pediatric studies. Two authors (A.P. and R.S.) independently assessed selected studies for the final analysis, with disagreements resolved by consensus with a third author (G.L.). If the article did not include data on mortality or was not full-text, the corresponding author was contacted for further data. No language restrictions were imposed.

Data Abstraction

One author (A.P.) extracted relevant information from each selected study. These data were checked by another author (R.S.). Disagreement was resolved by consensus with a third author (G.L.). We specifically extracted potential sources of significant clinical heterogeneity (*e.g.*, study design, clinical setting, inclusion and exclusion criteria, blood purification regimen).

The primary endpoint of this review was mortality at the longest follow-up available, and the secondary endpoint was mortality at 28 to 30 days.

Quality Assessment

Two authors (A.P. and R.S.) independently assessed the internal validity of each included trial according to the Cochrane Collaboration methods.^{19,20} We assessed the risk of bias associated with the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other bias. The other bias domain included the classic items reported by the “Cochrane Handbook for Systematic Reviews of

Interventions”¹⁹ but also the presence of an intention-to-treat analysis, sample size calculation, and ethical approval of the trial. If one or more of the domains were judged as having a high or unclear risk of bias, we classified the trial as having a high risk of bias. Due to the nature of the intervention, blinding of participants and personnel seemed difficult and was therefore not judged as crucial for bias assessment. We evaluated the potential risk of bias by applying a rating of “Low,” “High,” or “Unclear” to each study.

Two authors (A.P. and R.S.) independently reviewed the presence of authors’ possible conflict of interest and the funding source for each study, then rated each trial as of “Low,” “High,” or “Unclear” risk regarding those specific points.

The certainty of the body of evidence was assessed using the grading of recommendations assessment, development, and evaluation framework.^{21,22} The grading of recommendations assessment, development, and evaluation framework characterizes the certainty of a body of evidence on the basis of study limitations, imprecision, inconsistency, indirectness, and other considerations.

Statistical Analysis

Individual trial and summary results were reported as relative risk with 95% CI. We used a random-effects model except in cases where few trials dominated the available evidence or where significant publication bias was present, as random-effects meta-analysis applied in these contexts may give inappropriately high weight to smaller studies. Statistical heterogeneity was explored by the Cochran Q statistic and characterized using the I^2 metric. Publication bias was assessed by visually inspecting the funnel plot for the primary outcome. Statistical significance was set at $P = 0.05$. The meta-analysis was performed using Review Manager (RevMan, version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

The primary analysis was stratified by blood purification technique: hemoperfusion, hemofiltration, hemoperfusion combined with hemofiltration, or plasmapheresis. Hemoperfusion subgroup analyses including trials on polymyxin B immobilized fiber column hemoperfusion or hemoperfusion with other devices were carried out. To explore the sources of heterogeneity, we performed some subgroup analyses: (1) low risk of bias *versus* unclear/high risk of bias trials; (2) trials conducted in Asia *versus* Europe and America; (3) trials from the Nakamura group *versus* other trials; and (4) trials published after 2010 *versus* older trials.

To explore the relationship between treatment effect and disease severity, we performed various analyses: (1) a random-effects meta-regression on the APACHE II (Acute Physiology, Age, Chronic Health Evaluation II) score,²³ sepsis-related organ failure assessment score,²⁴ and control group mortality;¹⁴ (2) subgroup analyses according to conventional therapy group mortality: low-risk group (mortality rate less than 30%), intermediate-risk group (30 to

60%), and high-risk group (greater than 60%).¹⁴ We also performed a meta-regression for age to investigate a possible influence on outcome estimates. Finally, sensitivity analyses were performed by analyzing the data with a fixed or random effects model and using other summary statistics.

We performed a predefined random-effects trial sequential analysis,^{25–27} with the intent of maintaining an overall 5% risk of type I error and a 10% risk of type II error. We assumed a relative risk reduction of 15% and derived the control event proportion from the actual dataset. The resulting required information size was further diversity (D^2)-adjusted. In case of $D^2 = 0$ we performed a sensitivity analysis assuming a $D^2 = 25\%$. We used the trial sequential analysis software (TSAViewer [Computer program], version 0.9.5.5 Beta, Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, 2016). Deviations from the initial protocol are reported in the supplement (Supplemental Digital Content, eMethods 1, <http://links.lww.com/ALN/B977>).

Results

Search Results and Study Characteristics

The search strategy identified 6,933 citations and, after exclusion of inadequate reports (Supplemental Digital Content, table S3, <http://links.lww.com/ALN/B977>), 37 trials with 2,499 patients were included in the meta-analysis (fig. 1).^{17,28–63}

The characteristics of the included studies are shown in table 1 and in the supplement (Supplemental Digital Content, tables S4–S6, <http://links.lww.com/ALN/B977>). Two trials had four treatment arms.^{43,58} Twenty trials used a hemoperfusion technique, 13 used hemofiltration or hemodiafiltration, 4 trials combined hemofiltration with hemoperfusion, and 2 trials used plasma exchange. In three cases we received further information from corresponding authors.^{17,59,62}

Three trials were judged to be at low risk of bias,^{17,30,46} 20 at unclear risk, and 14 at high risk (Supplemental Digital Content, figs. S1 and S2, <http://links.lww.com/ALN/B977>). The grading of recommendations assessment, development, and evaluation assessment is reported in table S7 in the Supplemental Digital Content (<http://links.lww.com/ALN/B977>).

Hemoperfusion Techniques

Hemoperfusion (20 trials and 1,548 patients), which comprises various techniques differing among other things on the presence or absence of polymyxin B in the treatment regimen, was associated with a lower mortality compared to the control group (relative risk = 0.87 [95% CI, 0.78 to 0.98], $P = 0.02$, trial sequential analysis inconclusive, very low-certainty evidence) the analysis was limited by publication bias, small trial effects, and high heterogeneity (Supplemental Digital Content, figs S3–S5 and table S8, <http://links.lww.com/ALN/B977>). Subanalyses are reported in the

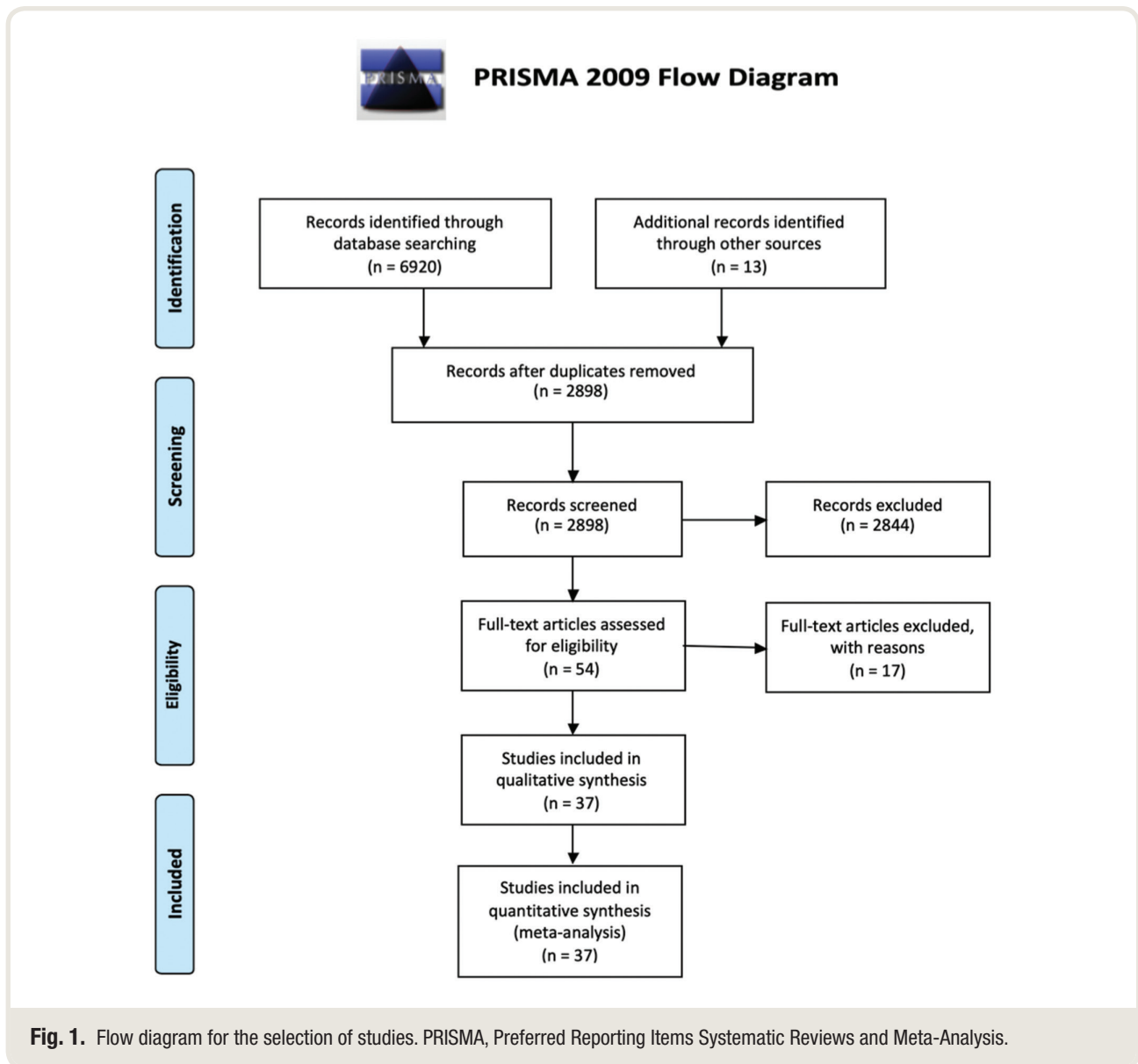


Fig. 1. Flow diagram for the selection of studies. PRISMA, Preferred Reporting Items Systematic Reviews and Meta-Analysis.

supplement (Supplemental Digital Content, figs. S6—S9 and eResults 1, <http://links.lww.com/ALN/B977>).

Polymyxin B Immobilized Fiber Column Hemoperfusion. Polymyxin B immobilized fiber column hemoperfusion (13 trials and 1,163 patients) was associated with a lower mortality at longest follow-up available compared to control (relative risk = 0.87 [95% CI, 0.77 to 0.98], $P = 0.03$, very low-certainty evidence), although the analysis was limited by very high heterogeneity ($I^2 = 74\%$, $P_{\text{heterogeneity}} < 0.001$) (fig. 2). No significant difference in 30-day mortality was found (Supplemental Digital Content, fig. S9, <http://links.lww.com/ALN/B977>).

Low risk of bias trials (three trials and 745 patients) found no difference in mortality with polymyxin B immobilized fiber column hemoperfusion *versus* control

(relative risk = 1.14 [95% CI, 0.96 to 1.36], $P = 0.12$, moderate-certainty evidence; fig. 2). Recent trials published after 2010 (three trials and 740 patients) showed that polymyxin B immobilized fiber column hemoperfusion was associated with higher mortality than conventional therapy (relative risk = 1.22 [95% CI, 1.03 to 1.45], $P = 0.02$, $I^2 = 0\%$, low-certainty evidence), while trials published before 2011 were associated with a mortality benefit (relative risk = 0.58 [95% CI, 0.49 to 0.69], $P < 0.001$, $I^2 = 8\%$; $P_{\text{groups}} < 0.001$). Studies conducted in Asia (seven trials in Japan and one in Thailand, with a total of 367 patients) showed that polymyxin B immobilized fiber column hemoperfusion decreased mortality (relative risk = 0.62 [95% CI, 0.52 to 0.75], $P < 0.001$, $I^2 = 57\%$, $P_{\text{heterogeneity}} = 0.02$), while aggregate data from trials conducted in the United States and Europe (five trials and 796

Table 1. Trials Characteristics

Trial	Country	Sample Size	Major Inclusion Criteria	Blood Purification Technique	Treatment Duration	Control Group Mortality	Risk of Bias
Hemoperfusion							
Polymyxin B-immobilized filter column hemoperfusion							
Cantaluppi 2008	Italy	16	Sepsis with positive culture for Gram-negative bacteria	PMX-HP	2 sessions of 2 h at 24-h interval	38%	Unclear
Cruz 2009	Italy	64	Severe sepsis or septic shock from an abdominal source	PMX-HP	2 sessions of 2 h at 24-h interval	67%	Low
Dellinger 2018	USA and Canada	449	Septic shock and an high endotoxin activity assay level	PMX-HP	2 sessions of 2 h at 24-h interval	42%	Low
Nakamura 1999	Japan	50	Septic shock	PMX-HP	2 sessions of 2 h at 24-h distance	70%	Unclear
Nakamura 2002(a)	Japan	18	Sepsis and trauma	PMX-HP	2 sessions of 2 h at 24-h interval	78%	Unclear
Nakamura 2002(b)	Japan	14	Sepsis	PMX-HP	2 sessions of 2 h at 24-h interval	86%	Unclear
Nakamura 2003(a)	Japan	20	Sepsis and MRSA-associated glomerulonephritis	PMX-HP	2 sessions of 2 h at 24-h interval	80%	Unclear
Nakamura 2003(b)	Japan	60	MRSA sepsis	PMX-HP	2 sessions of 2 h at 24-h interval	64%	Unclear
Nemoto 2001	Japan	98	Sepsis, severe sepsis, or septic shock	PMX-HP	1 or 2 sessions of 4 h	89%	Unclear
Payen 2015	France	232	Septic shock from and abdominal source	PMX-HP	2 sessions of 1.5 h at 22–24-h interval	24%	Low
Srisawat 2018	Thailand	59	Severe sepsis or septic shock, high endotoxin activity assay level, mostly under renal replacement therapy	PMX-HP	2 sessions of 2 h at 24-h interval	50%	High
Suzuki 2002	Japan	48	Septic shock	PMX-HP	1 HP session of 4 h, then 1 CVVHDF session until 24 h	75%	Unclear
Vincent 2005	Europe	35	Severe sepsis or septic shock from an intraabdominal source	PMX-HP	1 session of 2 h	28%	Unclear
Other hemoperfusion devices							
Hawchar 2019	Hungary	20	Septic shock of medical origin	HP with CytoSorb	1 session of 24 h	20%	High
Huang 2010	China	44	Severe sepsis or septic shock	HP with HA330 resin cartridge (Lizhu Industries, China)	3 sessions of 2 h at 24-h interval	55%	Unclear
Huang 2013	China	46	Severe sepsis or septic shock with acute lung injury from extrapulmonary source	HP with HA330 resin cartridge	3 sessions of 2 h at 24-h interval	67%	High
Reinhart 2004	Europe	143	Severe sepsis or septic shock	HP with Matisse EN500 endotoxin adsorber (Fresenius HemoCare Adsorber Technology GmbH, Germany).	A daily session for the first 4 d	25%	High
Schädler 2017	Germany	97	Severe sepsis or septic shock and ALI/ARDS	HP with CytoSorb	1 daily session of 6 h up to 7 d	26%	High
Shum 2014	China	15	Septic shock from an intra-abdominal source	HP with Alteco endotoxin hemoadsorber (Alteco Medical AB, Sweden)	2 sessions of 2 h at 24-h interval	25%	High
Zheng 2017	China	20	Sepsis, severe sepsis, or septic shock	HP with Adsorba 300 filter (manufacturer not reported)	1 HP session of 2.5 h	80%	Unclear
Hemofiltration							
Chung 2017	USA	37	Septic shock and burn	CVWH	nr	57%	Unclear
Cole 2002	nr	24	Severe sepsis with end-organ dysfunction or septic shock	CVWH with AN69 Filtral 12 filter (Hospal, France)	1 session of 2 d	33%	Unclear
Guo 2017	China	22	Severe sepsis or septic shock	CVWH with AN69 filter	1 session of 2 d	45%	Unclear
Han 2011	China	45	Severe sepsis	CVWH with AN69 filter	1 session of 3 d	41%	Unclear
Jing 2015	China	97	Severe sepsis or septic shock	CVWH	1 session of at least 3 d	37%	High

(Continued)

Table 1. (Continued)

Trial	Country	Sample Size	Major Inclusion Criteria	Blood Purification Technique	Treatment Duration	Control Group Mortality	Risk of Bias
Meng 2016	China	56	Septic shock and ARDS	CVWH with AN69 filter (Gambro Industries, France)	1 session of 3 d	32%	High
Payen 2009	France	76	Severe sepsis or septic shock	CVWH with Duraflo II filter (Edwards Lifesciences, USA)	1 session of at least 4 d	44%	Unclear
Peng 2010	China	22	Severe sepsis	CVWH with AN69 filter	1 session of 3 d	18%	Unclear
Quenot 2015	France	60	Septic shock	CVWH	1 session of 2 d	48%	High
Sander 1997	Germany	26	Severe sepsis or septic shock	CVWH with AN69 Multiflow 60 filter (Hospal, France)	1 session of at least 2 d	92%	High
Wang 2009	China	89	Septic shock	CVWH	1 session of 7 d	17	Unclear
Xu 2014	China	22	Sepsis and burn	CVWHDF	1 session of 12 h	18%	Unclear
Zheng 2017	China	20	Sepsis, severe sepsis, or septic shock	CVWH with M100 set (manufacturer not reported)	1 session of 24 h	80%	Unclear
Combined hemofiltration and hemoperfusion							
Hassan 2013	Malaysia	23	Severe sepsis or septic shock	CPFA with DF-140 (Infomed, Switzerland)	1 session of 24 h or until clinical improvement	83%	High
Livigni 2014	Italy	184	Septic shock	CPFA with Lynda (Bellco, Italy)	5 session of at least 10 h, in 5 consecutive days	49%	Unclear
Peng 2005	China	20	Sepsis and burn	CVWH with AN69 Multiflow-60 filter (manufacturer not reported) + PMX-HP	nr	20%	Unclear
Zheng 2017	China	20	Sepsis, severe sepsis, or septic shock	CVWH with M100 filter + HP with Adsorba-300 (manufacturers not reported)	1 CVWH-session of 24 h and 1 HP session of 2.5 h	80%	Unclear
Plasmapheresis							
Busund 2002	Russia	106	Severe sepsis or septic shock	na	2 sessions of about 2 h in 24 h	54%	High
Reeves 1999	Australia	22	Severe sepsis	na	1 session of 36 h	46%	Unclear

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CVWH, continuous veno-venous hemofiltration; CVWHDF, continuous veno-venous hemodiafiltration; CPFA, coupled plasma filtration adsorption; HP, hemoperfusion; MRSA, methicillin-resistant *Staphylococcus aureus*; PMX, polymyxin B-immobilized fiber column; na, not applicable; nr, not reported.

patients) found no difference (relative risk = 1.11 [95% CI, 0.94 to 1.32], $P = 0.21$, $I^2 = 50\%$, $P_{\text{heterogeneity}} = 0.09$), ($P_{\text{groups}} < 0.001$). Similarly, when excluding trials performed in Japan by the Nakamura group (five trials and 162 overall patients), polymyxin B immobilized fiber column hemoperfusion was associated with no difference in mortality compared to conventional therapy (relative risk = 0.98 [95% CI, 0.86 to 1.12], $P = 0.80$; Supplemental Digital Content, figs. S10–S13, <http://links.lww.com/ALN/B977>).

Hemoperfusion with Other Devices. Hemoperfusion with devices other than polymyxin B-immobilized filter column (seven trials and 385 patients) was not associated with a difference in mortality compared to conventional therapy (relative risk = 0.81 [95% CI, 0.53 to 1.21], $P = 0.30$, very low-certainty evidence). The

hemoperfusion devices included were Adsorba-300 filter (one trial, relative risk = 0.50 [95% CI, 0.22 to 1.14], $P = 0.10$); Alteco endotoxin hemoadsorber (one trial, relative risk = 0.57 [95% CI, 0.06 to 5.03], $P = 0.61$); CytoSorb (two trials, relative risk = 0.94 [95% CI, 0.14 to 6.49], $P = 0.95$); HA330 resin cartridge (two trials, relative risk = 0.61 [95% CI, 0.31 to 1.19], $P = 0.15$); and Matisse EN 500 endotoxin adsorber (one trial, relative risk = 1.13 [95% CI, 0.66 to 1.96], $P = 0.65$; Supplemental Digital Content, fig. S3, <http://links.lww.com/ALN/B977>).

Hemofiltration Techniques

The use of hemofiltration with a blood purification aim was associated with lower mortality compared to control

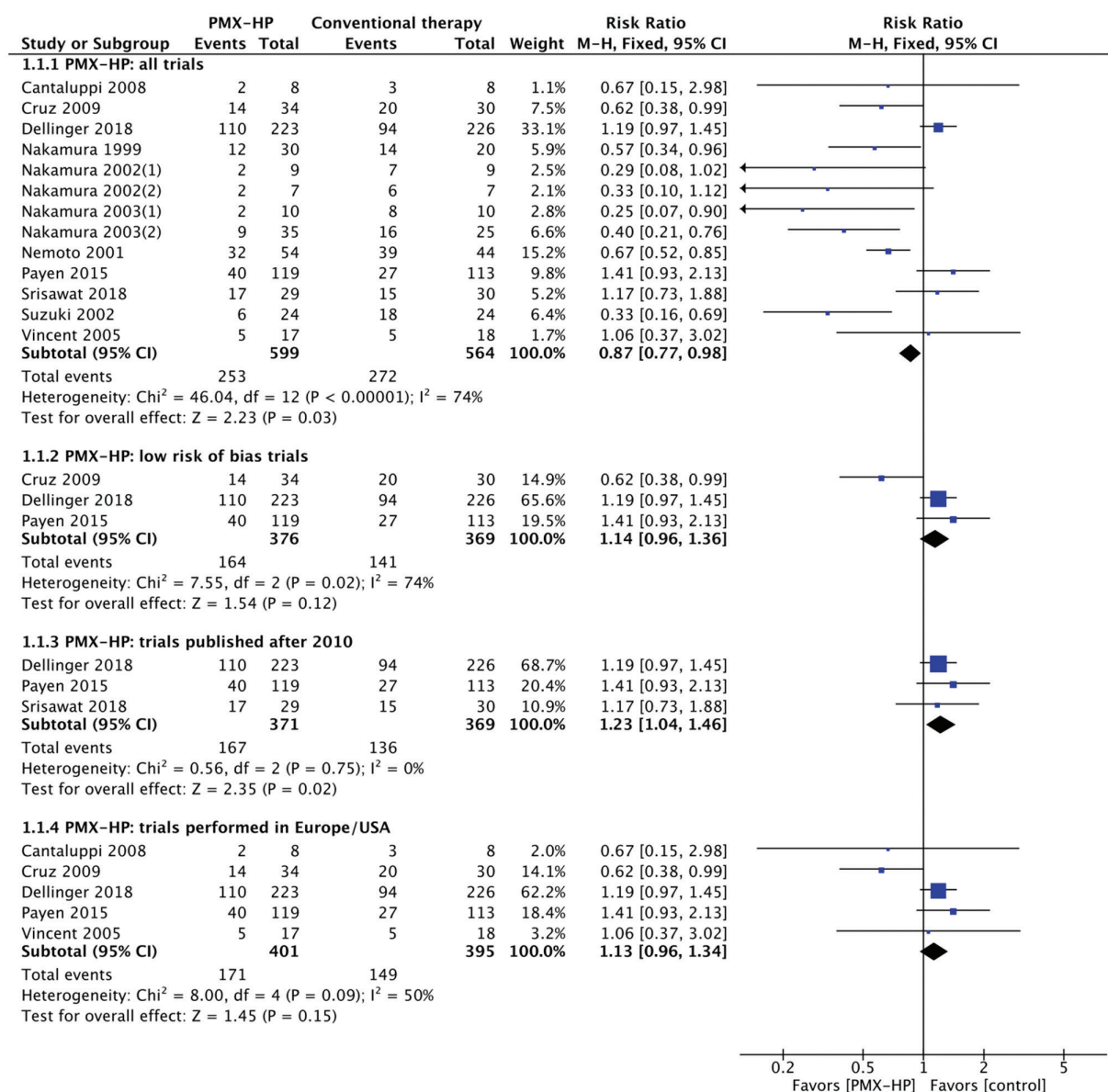


Fig. 2. Forest plot of the relative risk of mortality at longest follow up available with polymyxin B-immobilized fiber column hemoperfusion. Various subanalyses are also reported. M-H, Mantel-Haenszel; PMX-HP, polymyxin B immobilized fiber column hemoperfusion.

(relative risk = 0.79 [95% CI, 0.63, 1.00], $P = 0.05$, trial sequential analysis inconclusive, very low-certainty evidence) in 13 trials and 596 patients without acute kidney injury requiring renal replacement therapy (fig. 3 and Supplemental Digital Content, fig. S14, <http://links.lww.com/ALN/B977>). On subgroup analysis, hemofiltration was not associated with a difference in mortality in trials conducted in Europe and the United States (relative risk = 0.94 [95% CI, 0.74 to 1.19], $P = 0.61$, $I^2 = 0\%$, five trials and 223 patients) but was associated with a decrease in mortality in trials conducted in Asia (relative

risk = 0.58 [95% CI, 0.40 to 0.82], $P = 0.002$, $I^2 = 0\%$, eight trials and 373 patients; $P_{\text{groups}} = 0.02$); other analyses are reported in the supplement (Supplemental Digital Content, figs. S15–S18, table S9 and eResults 2, <http://links.lww.com/ALN/B977>).

Combined Hemofiltration and Hemoperfusion Techniques

The association of hemoperfusion and hemofiltration was not associated with a significant difference in mortality compared to control (relative risk = 0.63 [95% CI, 0.36 to 1.13], $P = 0.12$, trial sequential analysis inconclusive, very

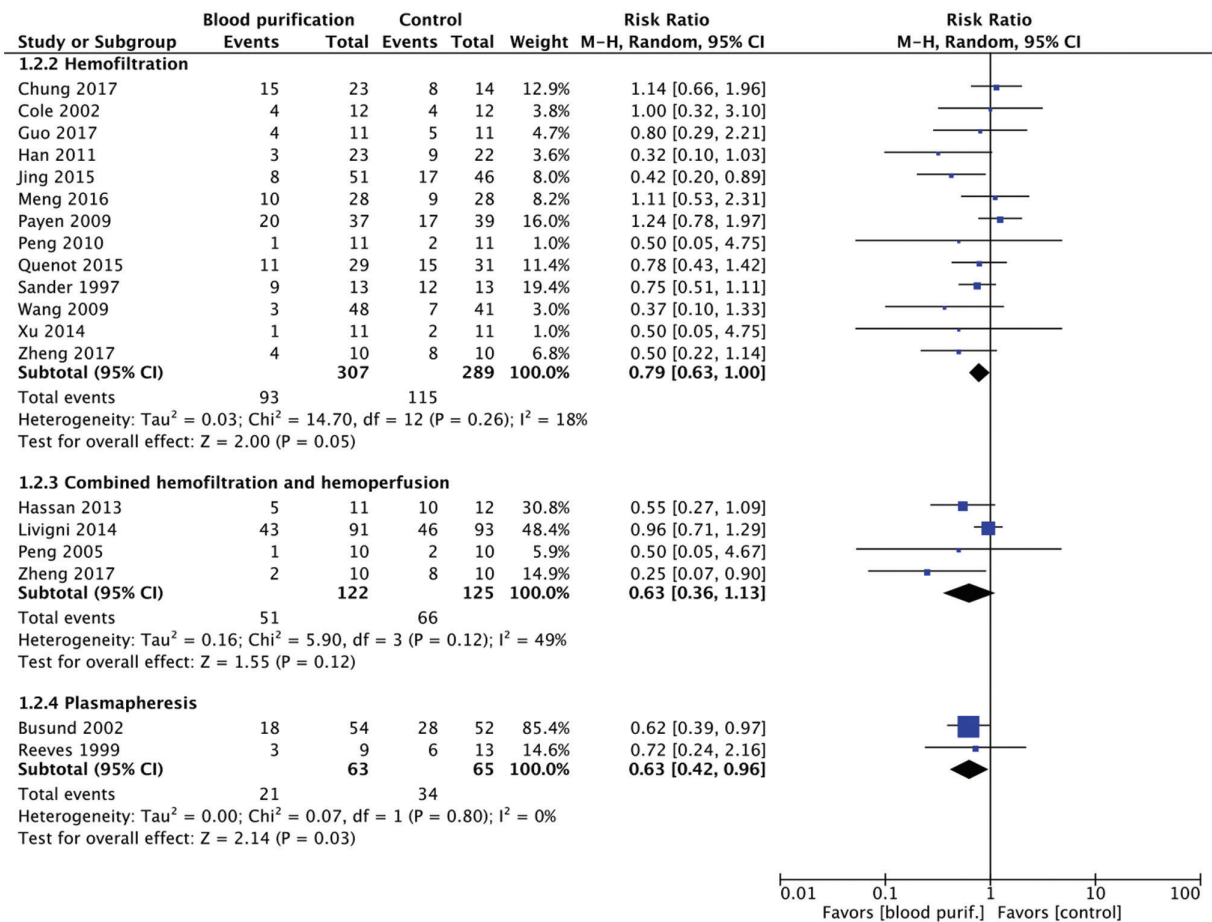


Fig. 3. Forest plot of the relative risk of mortality at the longest follow-up available with hemofiltration, combined hemofiltration and hemoperfusion, or plasmapheresis. Blood purif., blood purification; M-H, Mantel-Haenszel.

low-certainty evidence) in four trials including a total of 247 patients without acute kidney injury requiring renal replacement therapy (fig. 3).

Plasmapheresis Techniques

Plasmapheresis was associated with a lower mortality compared to standard treatment (relative risk = 0.63 [95% CI, 0.42 to 0.96], $P = 0.03$, trial sequential analysis inconclusive, very low-certainty evidence) with two trials and 128 patients included (fig. 3).

Discussion

We performed a comprehensive systematic review and meta-analysis on the mortality effects of blood purification with extracorporeal techniques in sepsis. The certainty of evidence underlying the use of blood purification therapies in sepsis is very low, and does not support their systematic use in patients with sepsis with or without septic shock.

Hemoperfusion

A variety of hemoperfusion techniques exists. Only a few randomized clinical trials were published on hemoperfusion techniques other than polymyxin B-immobilized filter column (*e.g.*, CytoSorb, Altec endotoxin hemoadsorber), suggesting the need for further clinical trials. However, polymyxin B immobilized fiber column hemoperfusion emerged as a promising therapy in septic shock with elevated endotoxin levels, and several studies were published on the topic in the past 20 yr. This technique consists of using a sorbent cartridge containing fibers coated with polymyxin B, an antibiotic with high affinity for lipopolysaccharide.⁹ Lipopolysaccharide is a cell wall component in Gram-negative bacteria that acts as an endotoxin by stimulating the production of inflammatory mediators by macrophages in a dose-dependent way and enhancing the inflammatory response.^{9,64} Endotoxemia seems to be more pronounced when tissue hypoperfusion is present and lipopolysaccharide blood levels seem to correlate with sepsis severity.^{9,65} Promising results in

pilot studies showed improvement in inflammatory mediators,¹⁰ cardiac and renal dysfunction,⁵⁶ hemodynamics, organ dysfunction, and 28-day mortality³⁰ in patients with abdominal septic shock. All these promising findings, together with the significant increase in arterial pressure after therapy initiation,^{15,17,30} made polymyxin B immobilized fiber column hemoperfusion an attractive therapy for clinicians. Conversely, recent large high-quality trials such as the EUPHRATES (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled trial of Adults Treated for Endotoxemia and Septic Shock)¹⁷ and the ABDO-MIX (Effects of Hemoperfusion With a Polymyxin B Membrane in Peritonitis With Septic Shock) group⁴⁶ trials yielded inconclusive results and reported a nonsignificant increase in mortality with polymyxin B immobilized fiber column hemoperfusion at the longest follow-up assessed.

The EUPHRATES trial, which is the largest and highest-quality randomized clinical trial performed so far, randomized 450 patients with septic shock and a high endotoxin activity assay level to two sessions of polymyxin B immobilized fiber column hemoperfusion of 90 to 120 min at a 24 h distance or to a sham treatment aiming at reducing 28-day mortality. The trial found no significant difference in the primary endpoint in the overall population or in the higher disease severity subgroup.¹⁷

Our meta-analysis including 13 trials on polymyxin B immobilized fiber column hemoperfusion is the largest and most comprehensive to date. Recently, some meta-analyses^{14,15,66} on polymyxin B immobilized fiber column hemoperfusion have appeared but failed to include some old and new randomized clinical trials. A meta-analysis concluded that this therapy may reduce mortality in patients with severe sepsis and septic shock in high disease severity subgroups based upon the aggregate analysis of 12 non-randomized trials and 5 small randomized clinical trials representing a very low-quality evidence.¹⁴ Two other meta-analyses respectively including only six and seven randomized clinical trials concluded that only low-quality evidence supported polymyxin B immobilized fiber column hemoperfusion for mortality reduction in sepsis.^{15,66} Since the release of EUPHRATES and other trials, a more comprehensive analysis was made possible. The positive results previously reported regarding polymyxin B immobilized fiber column hemoperfusion were driven by small randomized clinical trials conducted in Asia of low methodologic quality. Interestingly, when limiting the analysis to trials published after 2010 and including the two largest randomized clinical trials performed on the topic,^{17,46} polymyxin B immobilized fiber column hemoperfusion is associated with a higher mortality rate at the longest follow-up available. This together with inconclusive results on trial sequential analysis suggests that the current aggregate randomized evidence cannot consistently refute potential positive or detrimental effects on mortality. These findings

do not support the use of polymyxin B immobilized fiber column hemoperfusion in sepsis and septic shock.

Hemofiltration

The use of hemofiltration techniques as a blood purification treatment in patients without renal failure has also been suggested, with controversial results and insufficient evidence to recommend its use outside of experimental clinical settings.^{16,67} High-volume hemofiltration, further increasing plasma exchanges, was also investigated with limited results in patients with or without renal failure.^{29,68} We found a positive survival trend associated to hemofiltration, although those results are driven by small, low-quality randomized trials, and further investigation is therefore warranted.

Plasmapheresis

The first randomized clinical trial to ever address plasmapheresis as a blood purification technique reported a decrease in the intensity of acute-phase response.⁵⁰ A second randomized clinical trial with a larger sample population found an absolute mortality risk reduction of 20.5%.²⁸ Despite those promising results, the evidence is still too weak to recommend the use of plasmapheresis for blood purification in sepsis.⁶⁹

Disease Severity

Previous meta-analyses found that hemoperfusion was associated with a large positive effect in trials with a control group mortality rate greater than 60%, suggesting that hemoperfusion could be useful in the setting of higher disease severity.^{14,66} Our study yielded similar findings and also found a trend toward increased mortality in the lower disease severity subgroup (mortality less than 30%). Meta-regressions on APACHE II and sepsis-related organ failure assessment scores, both predictors of sepsis mortality, did not find any significant trend supporting those findings. Furthermore, most trials with a greater than 60% control group mortality are at unclear/high risk of bias, are small in size, and were conducted in Asia. In the EUPHRATES trial, the per-protocol subgroup analysis with high disease severity, including patients with a Multiple Organ Dysfunction Score greater than 9 at randomization and a control group 1-year mortality rate of 50%, was inconclusive and did not suggest any trend favoring polymyxin B immobilized fiber column hemoperfusion.¹⁷

Those inconsistencies make a beneficial effect of hemoperfusion or polymyxin B immobilized fiber column hemoperfusion in high-disease-severity patients unlikely. This specific question merits further investigation.

Future Directions

Current randomized evidence cannot support the use of extracorporeal blood purification techniques; further

trials are warranted before systemic implementation of these techniques. Furthermore, an increase in mortality related to extracorporeal therapies should not be excluded. Some randomized clinical trials describe a trend toward higher mortality with polymyxin B immobilized fiber column hemoperfusion⁴⁶ or CytoSorb-HP⁵⁴, for example. Numerically higher adverse events with polymyxin B immobilized fiber column hemoperfusion^{17,46} and greater disease severity with hemofiltration⁴⁵ were also reported. Our meta-analysis found an increased mortality at the longest follow-up available with polymyxin B immobilized fiber column hemoperfusion in a *post hoc* subgroup analysis including only the trials published after 2010. The unspecific removal of cytokines may remove mediators necessary to the function of the immune system, eventually provoking a deleterious outcome. Furthermore, the complex interaction between extracorporeal devices and inflammatory systems, micronutrients,⁷⁰ trace elements, electrolytes, and antibiotics levels and activity remain uninvestigated. Only few studies assessed the impact of those therapies on antibiotics, the only proven therapy in sepsis. A recent study on *in vitro* removal of anti-infective agents by CytoSorb-HP showed that all tested antibiotics were adsorbed by the cartridge in substantial amounts.⁷¹ The authors speculated that an additional dose within the first hours of treatment and therapeutic drug monitoring should be considered in this population.⁷¹ Similarly, an *in vitro* study assessing the effects of polymyxin B immobilized fiber column hemoperfusion on nine antibiotics reported adsorption of linezolid, suggesting a necessity for the monitoring of blood antimicrobial concentrations during polymyxin B immobilized fiber column hemoperfusion.^{72,73} A larger literature is present on hemofiltration, suggesting an increased antibiotic clearance with these devices.^{74–76}

Strengths and Limitations

We performed a comprehensive meta-analysis on blood purification techniques in sepsis and septic shock, which represents an important update to the literature in comparison to previous meta-analyses.^{13–16} Limitations of this study may appear similar to those of previous meta-analyses. Most included studies are small in size and at unclear or high risk of bias. Some studies assessed technical feasibility, but side effects were rarely reported, and a systematic assessment of adverse events is warranted in future trials. Heterogeneity in sepsis management, blood purification regimens (*e.g.*, modality, hemofiltration volume, duration of the session, filter and cartridge change, and so forth), and populations across different centers is evident, but we made an attempt at an exploration through several subanalyses in order to further assess the clinical potential of blood purification modalities in sepsis. The positive treatment effect found in trials conducted in Asia was also reported elsewhere¹³ and could be explained by publication bias, small studies effect, low methodologic quality, or a higher burden of disease as

suggested by the high control group mortality. Furthermore, seven polymyxin B immobilized fiber column hemoperfusion trials from Japan were performed before 2005, and the progress in conventional therapy management and outcome in the past years could have diluted or cancelled the beneficial effects of this treatment.

Conclusions

Very low-quality randomized evidence demonstrates that the use of hemoperfusion, hemofiltration, or plasmapheresis may reduce mortality in sepsis or septic shock. Moderate-certainty evidence supports that polymyxin B immobilized fiber column hemoperfusion is not associated with any significant difference in mortality in comparison to conventional treatment regimen. Detrimental effects on survival could not be excluded by aggregate randomized evidence. Further high-quality randomized controlled trials adequately powered for mortality are needed to assess the real impact of blood purification techniques before such therapies can be systematically implemented in clinical practice.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Landoni: Department of Cardiothoracic Anaesthesia and Intensive Care, Ospedale San Raffaele, Via Olgettina 60, Milano, 20132 Italy. landoni.giovanni@hsr.it. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801–10
2. Gaieski DE, Edwards JM, Kallan MJ, Carr BG: Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013; 41:1167–74

3. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R: Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014; 311:1308–16
4. Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y; ICON investigators: Assessment of the worldwide burden of critical illness: The Intensive Care Over Nations (ICON) audit. *Lancet Respir Med* 2014; 2:380–6
5. Angus DC, van der Poll T: Severe sepsis and septic shock. *N Engl J Med* 2013; 369:840–51
6. Jaffer U, Wade RG, Gourlay T: Cytokines in the systemic inflammatory response syndrome: A review. *HSR Proc Intensive Care Cardiovasc Anesth* 2010; 2:161–75
7. Villa G, Neri M, Bellomo R, Cerda J, Gaudio AR De, Rosa S De, Garzotto F, Honore PM, Kellum J, Lorenzin A, Payen D, Ricci Z, Samoni S, Vincent J-L, Wendon J, Zaccaria M, Ronco C, Nomenclature Standardization Initiative (NSI) Alliance: Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: Practical applications. *Crit Care* 2016; 20:283
8. Rimmelé T, Kellum JA: High-volume hemofiltration in the intensive care unit: A blood purification therapy. *ANESTHESIOLOGY* 2012; 116:1377–87
9. Ronco C, Klein DJ: Polymyxin B hemoperfusion: A mechanistic perspective. *Crit Care* 2014; 18:309
10. Kanesaka S, Sasaki J, Kuzume M, Narihara K, Takahashi Y: Effect of direct hemoperfusion using polymyxin B immobilized fiber on inflammatory mediators in patients with severe sepsis and septic shock. *Int J Artif Organs* 2008; 31:891–7
11. Poli EC, Rimmelé T, Schneider AG: Hemoadsorption with CytoSorb®. *Intensive Care Med* 2019; 45:236–9
12. Rimmelé T, Kellum JA: Clinical review: Blood purification for sepsis. *Crit Care* 2011; 15:205
13. Zhou F, Peng Z, Murugan R, Kellum JA: Blood purification and mortality in sepsis: A meta-analysis of randomized trials. *Crit Care Med* 2013; 41:2209–20
14. Chang T, Tu YK, Lee CT, Chao A, Huang CH, Wang MJ, Yeh YC: Effects of polymyxin B hemoperfusion on mortality in patients with severe sepsis and septic shock: A systemic review, meta-analysis update, and disease severity subgroup meta-analysis. *Crit Care Med* 2017; 45:e858–64
15. Fujii T, Ganeko R, Kataoka Y, Furukawa TA, Featherstone R, Doi K, Vincent JL, Pasero D, Robert R, Ronco C, Bagshaw SM: Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: A systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2018; 44:167–78
16. Putzu A, Fang MX, Boscolo Berto M, Belletti A, Cabrini L, Cassina T, Landoni G: Blood purification with continuous veno-venous hemofiltration in patients with sepsis or ARDS: A systematic review and meta-analysis. *Minerva Anesthesiol* 2017; 83:867–77
17. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, Palevsky PM, Weisberg LS, Schorr CA, Trzeciak S, Walker PM; EUPHRATES Trial Investigators: Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: The EUPHRATES randomized clinical trial. *JAMA* 2018; 320:1455–63
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009; 339:b2700
19. Higgins JPT, Green S (eds): *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: <http://handbook.cochrane.org>. Accessed May 27, 2019
20. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928
21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–6
22. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ: GRADE guidelines: 1. Introduction–GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64:383–94
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–29
24. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–10
25. Brok J, Thorlund K, Wetterslev J, Gluud C: Apparently conclusive meta-analyses may be inconclusive—Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently

- conclusive neonatal meta-analyses. *Int J Epidemiol* 2009; 38:287–98
26. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, Gluud LL, Als-Nielsen B, Gluud C: Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol* 2009; 38:276–86
 27. Thorlund K, Engström J, Wetterslev J, Brok J, Imberger G, Gluud C: User Manual for Trial Sequential Analysis (TSA). Copenhagen, Denmark, Copenhagen Trial Unit, Centre for Clinical Intervention Research, 2011. Available at: <http://www.ctu.dk/tsa>. Accessed May 27, 2019
 28. Busund R, Koukline V, Utrobin U, Nedashkovsky E: Plasmapheresis in severe sepsis and septic shock: A prospective, randomised, controlled trial. *Intensive Care Med* 2002; 28:1434–9
 29. Chung KK, Coates EC, Smith DJ Jr, Karlinski RA, Hickerson WL, Arnold-Ross AL, Mosier MJ, Halerz M, Sprague AM, Mullins RE, Caruso DM, Albrecht M, Arnold BD, Burris AM, Taylor SL, Wolf SE; Randomized controlled Evaluation of high-volume hemofiltration in adult burn patients with Septic shock and acute kidney injury (RESCUE) Investigators: High-volume hemofiltration in adult burn patients with septic shock and acute kidney injury: A multicenter randomized controlled trial. *Crit Care* 2017; 21:289
 30. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Bobbio Pallavicini FM, Rottoli F, Giunta F, Ronco C: Early use of polymyxin B hemoperfusion in abdominal septic shock: The EUPHAS randomized controlled trial. *JAMA* 2009; 301:2445–52
 31. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C: A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med* 2002; 30:100–6
 32. Guo J, Tao W, Tang D, Zhang J: Th17/regulatory T cell imbalance in sepsis patients with multiple organ dysfunction syndrome: Attenuated by high-volume hemofiltration. *Int J Artif Organs* 2017; 40:607–14
 33. Hassan J, Cader RA, Kong NC, Mohd M, Rahman AR, Hod R: Coupled plasma filtration adsorption (CPFA) plus continuous veno-venous haemofiltration (CVVH) versus CVVH alone as an adjunctive therapy in the treatment of sepsis. *EXCLI J* 2013; 12:681–92
 34. Huang Z, Wang SR, Yang ZL, Liu JY: Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. *Ther Apher Dial* 2013; 17:454–61
 35. Huang Z, Wang SR, Su W, Liu JY: Removal of humoral mediators and the effect on the survival of septic patients by hemoperfusion with neutral microporous resin column. *Ther Apher Dial* 2010; 14:596–602
 36. Jing F, Wang J, Li M, Chu YF, Jiang JJ, Ding M, Wang YP, Wang CT, Ren HS: The influence of high volume hemofiltration on extra vascular lung water and alveolar-arterial oxygen pressure difference in patients with severe sepsis. *Eur Rev Med Pharmacol Sci* 2015; 19:3792–800
 37. Livigni S, Bertolini G, Rossi C, Ferrari F, Giardino M, Pozzato M, Remuzzi G; GiViTI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units: Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial. *BMJ Open* 2014; 4:e003536
 38. Nakamura T, Ebihara I, Shoji H, Ushiyama C, Suzuki S, Koide H: Treatment with polymyxin B-immobilized fiber reduces platelet activation in septic shock patients: Decrease in plasma levels of soluble P-selectin, platelet factor 4 and beta-thromboglobulin. *Inflamm Res* 1999; 48:171–5
 39. Meng JB, Lai ZZ, Xu XJ, Ji CL, Hu MH, Zhang G: Effects of early continuous venovenous hemofiltration on E-selectin, hemodynamic stability, and ventilatory function in patients with septic-shock-induced acute respiratory distress syndrome. *Biomed Res Int* 2016; 2016:7463130
 40. Nakamura T, Ushiyama C, Suzuki Y, Shoji H, Shimada N, Koide H: Hemoperfusion with polymyxin B immobilized fibers for urinary albumin excretion in septic patients with trauma. *ASAIO J* 2002; 48:244–8
 41. Nakamura T, Ushiyama C, Shoji H, Koide H: Effects of hemoperfusion on serum cardiac troponin T concentrations using polymyxin B-immobilized fibers in septic patients undergoing hemodialysis. *ASAIO J* 2002; 48:41–4
 42. Nakamura T, Ushiyama C, Suzuki Y, Osada S, Inoue T, Shoji H, Hara M, Shimada N, Koide H: Hemoperfusion with polymyxin B-immobilized fiber in septic patients with methicillin-resistant *Staphylococcus aureus*-associated glomerulonephritis. *Nephron Clin Pract* 2003; 94:c33–9
 43. Nakamura T, Ushiyama C, Suzuki Y, Inoue T, Shoji H, Shimada N, Koide H: Combination therapy with polymyxin B-immobilized fibre haemoperfusion and teicoplanin for sepsis due to methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 2003; 53:58–63
 44. Nemoto H, Nakamoto H, Okada H, Sugahara S, Moriwaki K, Arai M, Kanno Y, Suzuki H: Newly developed immobilized polymyxin B fibers improve the survival of patients with sepsis. *Blood Purif* 2001; 19:361–8; discussion 368–9
 45. Payen D, Mateo J, Cavaillon JM, Fraise F, Floriot C, Vicaut E; Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine

- d'Urgence des Hôpitaux extra-Universitaires: Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial. *Crit Care Med* 2009; 37:803–10
46. Payen DM, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, Pottecher J, Joannes-Boyau O, Martin-Lefevre L, Jabaudon M, Mimoz O, Coudroy R, Ferrandière M, Kipnis E, Vela C, Chevallier S, Mallat J, Robert R; ABDOMIX Group: Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: A multicenter randomized control trial. *Intensive Care Med* 2015; 41:975–84
 47. Peng Y, Yuan Z, Li H: Removal of inflammatory cytokines and endotoxin by veno-venous continuous renal replacement therapy for burned patients with sepsis. *Burns* 2005; 31:623–8
 48. Peng Z, Pai P, Hong-Bao L, Rong L, Han-Min W, Chen H: The impacts of continuous veno-venous hemofiltration on plasma cytokines and monocyte human leukocyte antigen-DR expression in septic patients. *Cytokine* 2010; 50:186–91
 49. Quenot JP, Binquet C, Vinsonneau C, Barbar SD, Vinault S, Deckert V, Lemaire S, Hassain AA, Bruyère R, Souweine B, Lagrost L, Adrie C: Very high volume hemofiltration with the Cascade system in septic shock patients. *Intensive Care Med* 2015; 41:2111–20
 50. Reeves JH, Butt WW, Shann F, Layton JE, Stewart A, Waring PM, Presneill JJ: Continuous plasmafiltration in sepsis syndrome. *Plasmafiltration in Sepsis Study Group*. *Crit Care Med* 1999; 27:2096–104
 51. Reinhart K, Meier-Hellmann A, Beale R, Forst H, Boehm D, Willatts S, Rothe KF, Adolph M, Hoffmann JE, Boehme M, Bredle DL; EASy-Study Group: Open randomized phase II trial of an extracorporeal endotoxin adsorber in suspected Gram-negative sepsis. *Crit Care Med* 2004; 32:1662–8
 52. Sander A, Armbruster W, Sander B, Daul AE, Lange R, Peters J: Hemofiltration increases IL-6 clearance in early systemic inflammatory response syndrome but does not alter IL-6 and TNF alpha plasma concentrations. *Intensive Care Med* 1997; 23:878–84
 53. Shum HP, Leung YW, Lam SM, Chan KC, Yan WW: Alteco endotoxin hemoabsorption in Gram-negative septic shock patients. *Indian J Crit Care Med* 2014; 18:783–8
 54. Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK: The effect of a novel extracorporeal cytokine hemoabsorption device on IL-6 elimination in septic patients: A randomized controlled trial. *PLoS One* 2017; 12:e0187015
 55. Suzuki H, Nemoto H, Nakamoto H, Okada H, Sugahara S, Kanno Y, Moriwaki K: Continuous hemodiafiltration with polymyxin-B immobilized fiber is effective in patients with sepsis syndrome and acute renal failure. *Ther Apher* 2002; 6:234–40
 56. Vincent JL, Laterre PF, Cohen J, Burchardi H, Bruining H, Lerma FA, Wittebole X, De Backer D, Brett S, Marzo D, Nakamura H, John S: A pilot-controlled study of a polymyxin B-immobilized hemoperfusion cartridge in patients with severe sepsis secondary to intra-abdominal infection. *Shock* 2005; 23:400–5
 57. Xu C, Fan K, Xie L, Chen W, Wang L: Evaluation of optimized continuous venovenous hemodiafiltration therapy efficiency in severe burn patients with sepsis. *Burns Trauma* 2014; 2:125–9
 58. Zheng S, Weng Q, Wu W, Ding G: Blood purification treatment initiated at the time of sepsis diagnosis effectively attenuates serum HMGB1 upregulation and improves patient prognosis. *Exp Ther Med* 2017; 14:3029–35
 59. Hawchar F, László I, Öveges N, Trásy D, Ondrik Z, Molnar Z: Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study. *J Crit Care* 2019; 49:172–8
 60. Han SS, Sun T, Li Z, Jia LZ, Shang QM, Wang XZ: [Effect of continuous blood purification on endothelial cell function in patients with severe sepsis]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2011; 23:81–4
 61. Wang CT, Ren HS, Jiang JJ, Zhang JC, Meng M, Yu JB, Chu YF, Ding M: [Study the effects of high-volume hemofiltration and fluid resuscitation on removing blood lactic acid and pro-inflammatory cytokines in patients with refractory septic shock]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2009; 21:421–4
 62. Cantaluppi V, Assenzio B, Pasero D, Romanazzi GM, Pacitti A, Lanfranco G, Puntorieri V, Martin EL, Mascia L, Monti G, Casella G, Segoloni GP, Camussi G, Ranieri VM: Polymyxin-B hemoperfusion inactivates circulating proapoptotic factors. *Intensive Care Med* 2008; 34:1638–45
 63. Srisawat N, Tungsanga S, Lumlertgul N, Komaenthamsophon C, Peerapornratana S, Thamrongsat N, Tiranathanagul K, Praditpornsilpa K, Eiam-Ong S, Tungsanga K, Kellum JA: The effect of polymyxin B hemoperfusion on modulation of human leukocyte antigen DR in severe sepsis patients. *Crit Care* 2018; 22:279
 64. Casey LC, Balk RA, Bone RC: Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. *Ann Intern Med* 1993; 119:771–8
 65. Marshall JC, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, Opal S, Abraham E, Brett SJ, Smith T, Mehta S, Derzko A, Romaschin A; MEDIC study: Diagnostic and prognostic implications of endotoxemia in critical illness: Results of the MEDIC study. *J Infect Dis* 2004; 190:527–34

66. Terayama T, Yamakawa K, Umemura Y, Aihara M, Fujimi S: Polymyxin B hemoperfusion for sepsis and septic shock: A systematic review and meta-analysis. *Surg Infect (Larchmt)* 2017; 18:225–33
67. Vriese AS De, Colardyn FA, Philippé JJ, Vanholder RC, Sutter JH De, Lameire NH, H. DV, Lameire NH: Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol* 1999; 10:846–53
68. Borthwick EMJ, Hill CJ, Rabindranath KS, Maxwell AP, McAuley DE, Blackwood B: High-volume haemofiltration for sepsis. *Cochrane Database Syst Rev* 2013; 1:CD008075
69. Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, Rock G, Turgeon AF, Cook DJ, Houston DS, Zarychanski R: The efficacy and safety of plasma exchange in patients with sepsis and septic shock: A systematic review and meta-analysis. *Crit Care* 2014; 18:699
70. Berger MM, Shenkin A, Revely JP, Roberts E, Cayeux MC, Baines M, Chioléro RL: Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. *Am J Clin Nutr* 2004; 80:410–6
71. König C, Röhr AC, Frey OR, Brinkmann A, Roberts JA, Wichmann D, Braune S, Kluge S, Nierhaus A: In vitro removal of anti-infective agents by a novel cytokine adsorbent system. *Int J Artif Organs*. 2019; 42:57–64
72. Shimokawa K, Takakuwa R, Wada Y, Yamazaki N, Ishii F: Adsorption of various antimicrobial agents to endotoxin removal polymyxin-B immobilized fiber (Toraymyxin®). Part 2: Adsorption of two drugs to Toraymyxin PMX-20R cartridges. *Colloids Surf B Biointerfaces* 2013; 101:350–2
73. Shimokawa K, Takakuwa R, Taya K, Wada Y, Yamazaki N, Murata M, Hirata K, Masuno T, Yokota H, Ishii F: Adsorption of various antimicrobial agents to endotoxin removal polymyxin-B immobilized fiber (Toraymyxin®). *Colloids Surf B Biointerfaces* 2012; 90:58–61
74. Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L, Lipman J, Bellomo R; RENAL Replacement Therapy Study Investigators: Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: A multicentre pharmacokinetic study. *Crit Care Med* 2012; 40:1523–8
75. Kielstein JT, Burkhardt O: Dosing of antibiotics in critically ill patients undergoing renal replacement therapy. *Curr Pharm Biotechnol* 2011; 12:2015–9
76. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA: Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. *Ann Intensive Care* 2012; 2:35